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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/815,825 | 03/22/2001 | Keith D. Allen | R-849 | 6413 |

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| EXAMINER |
|---|
| SULLIVAN, DANIEL M |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | 18 |

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/815,825 | ALLEN ET AL. | |
| | Examiner | Art Unit | |
| | Daniel M Sullivan | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 June 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5,8-12,17-23,27-33,35,42,45 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *4* is/are allowed.

6)☒ Claim(s) *1-3,5,8-12,17-23,27-33,35,42,45 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

This Non-Final Office Action is a response to the "Response under 37 CFR §1.111" filed 5 June 2003 (Paper No. 16) in reply to the Non-Final Office Action mailed 2 December 2002 (Paper No. 15). Claims 1-5, 8-14, 17-23, 26-33, 35, 37, 39, 42 and 45-47 were considered in Paper No. 15. Claims 13, 14, 37, 39 and 46 were canceled and claims 1, 9-12, 20, 22, 23, 27, 32, 33, 35, 45 and 47 were amended in Paper No. 16. Claims 1-5, 8-12, 17-23, 27-33, 35, 42, 45 and 47 are pending and under consideration.

### *Response to Amendment*

Rejection of claims 13, 14, 37, 39 and 46 is rendered moot by cancellation of the claims.

Claim Objections

Objection to claims 27-31 is withdrawn.

Claim Rejections - 35 USC § 112, First Paragraph

Rejection of claims 1-5, 10, 12, 27-33, 45 and 47 under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claims for reasons set forth in the previous Office Actions is withdrawn.

Claims 10 and 23 stand rejected under 35 U.S.C. 112, first paragraph, as lacking enablement for the full scope of the claimed subject matter for reasons set forth in Paper No. 15. As stated in the previous office action, the disclosure is only enabling for the method

"comprising introducing a cGMP phosphodiesterase alpha subunit gene targeting construct into a mouse ES cell" (page 6; emphasis added). As the embryonic stem cell used in the method is not limited to a mouse embryonic stem cell, the claims still encompass subject matter that is not fully enabled by the disclosure.

Rejection of claims 12, 27-33, 45 and 47 under 35 U.S.C. § 112, first paragraph, as lacking adequate written description is withdrawn.

Claim Rejections - 35 USC § 112, Second Paragraph

Rejection of claims 9, 20, 22, 33, 45 and 47 under 35 U.S.C. 112, second paragraph, as indefinite is withdrawn.

Claim Rejections - 35 USC § 103

Rejection of claim 35 under 35 U.S.C. § 103(a) as unpatentable over Baehr *et al.* and Lem *et al.* and in further view of Tanabe *et al.* is withdrawn.

***New Grounds Necessitated by Amendment***

Claim Objections

Claim 1 is objected to because of the following informalities: There are two steps (b) in the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 12, 32 and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying an agent that ameliorates an abnormality associated with a homozygous disruption in a cGMP phosphodiesterase gene wherein said abnormality is an eye abnormality or hyperactive behavior relative to a wild type mouse, does not reasonably provide enablement for a method of identifying an agent that ameliorates any and all abnormalities associated with disruption of a cGMP phosphodiesterase alpha subunit gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

*Nature of the invention and Breadth of the claims*: The amended claims are now directed to methods of identifying an agent that ameliorates an abnormality associated with a disruption in a cGMP phosphodiesterase gene or disruption of cGMP phosphodiesterase expression. Although the animal used in the methods is limited to exhibiting an eye abnormality or hyperactivity, the determining step is not limited to measuring amelioration of said eye abnormality or hyperactivity. Therefore, the claims encompass methods of identifying an agent that ameliorates any abnormality associated with a disruption in a cGMP phosphodiesterase gene or disruption of cGMP phosphodiesterase expression regardless of whether the abnormality has been disclosed.

*State and level of predictability in the art*: The art teaches that, within mice, the phenotype arising from insertion or deletion of even a well-characterized gene is unpredictable. Doetchman (1999) *Lab. Animal Sci.* 49:137-143 teaches, "[o]ne often hears the comment that genetically engineered mice...are not useful because they frequently do not yield the expected phenotype, or they don't seem to have any phenotype. These expectations are often based on years of work, and in some instances, thousands of publications of mostly in vitro studies" (page 137, paragraph 1). Doetchman goes on to teach, "it has become clear that genetic background plays an important role in the susceptibility of mice to many disorders. Therefore, the phenotypes of knockout mouse strains will also have genetic background dependencies" (page 140, column 2, third full paragraph) and "[a]pparent lack of phenotype more likely reflects or inability to ask the right questions, or our lack of tools to answer them" page 142, first paragraph. These teachings point out that the phenotype arising from any given mutation or genetic manipulation

of a transgenic mouse is highly unpredictable and in some cases requires empirical experimentation to uncover.

*Amount of direction provided by the inventor and existence of working examples*: The instant disclosure provides that transgenic mice comprising homozygous disruption of the cGMP phosphodiesterase gene exhibit various eye abnormalities and hyperactive behavior relative to wild type mice, and that mice heterozygous for the disruption exhibit eye discoloration (pages 60-61). The specification provides no guidance that would enable the skilled artisan to identify an agent that ameliorates an abnormality other than those described in the specification. Furthermore, the disclosure provides no guidance that would enable the skilled artisan to identify abnormalities other than those described in the specification, which could be assayed for in the claimed method, without engaging in blind trial and error experimentation.

*Relative skill of those in the art and quantity of experimentation needed to make or use the invention*: The relative level of skill in the art is high. However, given the art-recognized unpredictability of the phenotype arising from a given genetic disruption, the skilled artisan would not be able to use the claimed methods to identify an agent that ameliorates an abnormality associated with disruption in a cGMP phosphodiesterase alpha gene, other than the disclosed eye abnormality or hyperactive behavior, without engaging in experimentation to identify the other abnormalities. Clearly the level of experimentation required to identify all abnormalities associated with disruption of a cGMP phosphodiesterase alpha gene would be beyond what is considered routine in the art. Therefore, only the methods wherein the abnormality measured in the determining step is an eye abnormality or hyperactivity relative to a wild type mouse are enabled by the specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is indefinite in the recitation of "the phenotype" in part (b). The claim depends from claim 8, which is directed to a mouse exhibiting a phenotype comprising an eye abnormality. Because open language (i.e., comprising) is used to describe the phenotype, it is unclear whether the phenotype referred to in claim 32 is limited to the eye abnormality or is directed to any phenotype including those also comprised by the mouse but not identified. In the interest of compact prosecution, the claim has been examined according to the broadest reasonable scope of "the phenotype", which is any phenotype comprised by the mouse of claim 8. This rejection can be overcome by clearly stating the phenotype to be determined in part (b) of the claim.

***New Grounds***

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5, 8-12, 17-23, 27-33, 35, 42, 45 and 47 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

It was previously indicated that cells and mice limited to comprising homozygous disruption of the cGMP phosphodiesterase alpha subunit gene and having a phenotype selected from an eye abnormality or hyperactivity are adequately described by the teachings of the specification. However, adequate written description of a transgenic mouse requires description of both the genotype and phenotype of the mouse.

In the instant case, the genotypes encompassed by "disruption" include mutations that enhance or alter the activity of the as well as inactivate the gene (see page 7 of the specification). Thus, claims directed to a transgenic mouse comprising homozygous disruption of a cGMP phosphodiesterase alpha subunit gene are generic to mice comprising a wide variety of genotypes. Although the mice are now limited to comprising a specific phenotype, the specification provides descriptive support only for a mouse comprising homozygous disruption of the cGMP phosphodiesterase alpha subunit, wherein production of the cGMP phosphodiesterase alpha subunit is completely inhibited. Given the unpredictability of phenotype arising from any particular phenotype, established in previous Office Actions, the skilled artisan would not know which genotypes encompassed by "disruption" of the cGMP phosphodiesterase alpha subunit would give rise to the phenotypes recited in the claims. Thus, the specification does not clearly allow persons of ordinary skill in the art to recognize that, as of the filing date

sought, Applicant was in possession of the full scope of the invention. Thus, only transgenic mice comprising homozygous disruption of the cGMP phosphodiesterase alpha subunit, wherein production of the cGMP phosphodiesterase alpha subunit is completely inhibited meet the written description requirement.

With regard to claim 5, only a mouse embryonic stem cell comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene, wherein production of the cGMP phosphodiesterase alpha subunit is completely inhibited and wherein a transgenic mouse produced from said stem cell exhibits a phenotype selected from an eye abnormality or hyperactive behavior, is adequately described by the disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in the recitation of "selectable marker" and "screening marker". It is unclear whether applicant intends that the claims be limited to a marker that can be detected directly or whether the vectors actually comprise genes encoding selectable or screening markers as is more commonly used in the art.

Amending the claims to indicate that the constructs comprise a "selectable marker gene" or a "screening marker gene" would obviate this objection.

***Allowable Subject Matter***

Claim 4 is allowed.

Claims 1-3 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER